# Peramivir IV Questions and Answers for Health Care Providers

## Q1. What action is FDA taking regarding Peramivir IV?

A. As part of the federal government's response to the 2009 H1N1 public health emergency, the Commissioner of the Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) authorizing the emergency use of the unapproved drug Peramivir IV, to treat certain hospitalized adult and pediatric patients with suspected **or** laboratory confirmed 2009 H1N1 infection **or** infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology.

This set of Questions and Answers is not intended to be a substitute for the comprehensive information about Peramivir IV contained in the Peramivir IV Fact Sheet for Health Care Providers or for the terms and conditions as set forth in the EUA.

## Q2. What is Peramivir IV?

A. Peramivir IV is an intravenous (IV) neuraminidase inhibitor that has a mechanism of action similar to the two approved neuraminidase inhibitors, Tamiflu (oseltamivir phosphate) capsules and for oral suspension and Relenza (zanamivir) Inhalation Powder, for oral inhalation. Neuraminidase inhibitors work by inhibiting the neuraminidase enzyme which affects the release of viral particles, thereby reducing the amount of virus in the body.

## Q3. What uses of Peramivir IV are authorized under the EUA?

A. Under the EUA, Peramivir IV is authorized for emergency use in the treatment of certain hospitalized patients with suspected or laboratory confirmed 2009 H1N1 infection or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology. Specifically, Peramivir IV is authorized only for the following patients who are admitted to a hospital and under the care or consultation of a licensed clinician (skilled in the diagnosis and management of patients with potentially life-threatening illness and the ability to recognize and manage medication-related adverse events):

- Adult patients for whom therapy with an IV agent is clinically appropriate, based upon one or more of the following reasons:
    - patient not responding to either oral or inhaled antiviral therapy, or
    - drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or
    - the clinician judges IV therapy is appropriate due to other circumstances.
- Pediatric patients for whom an IV agent is clinically appropriate because:
    - patient not responding to either oral or inhaled antiviral therapy, or
    - drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible.

FDA has authorized the emergency use of Peramivir IV under EUA based upon its conclusion that the statutory criteria for issuance of an EUA, summarized below, have been met:

- The 2009 H1N1 Influenza virus can cause influenza, a serious or life-threatening disease or condition;

- based on the totality of scientific evidence available to FDA, it is reasonable to believe that Peramivir IV may be effective for the treatment of 2009 H1N1 influenza in certain adult and pediatric patients;

- the known and potential benefits of Peramivir IV outweigh the known and potential risks of Peramivir IV for the treatment of 2009 H1N1 influenza in certain adult and pediatric patients; and

- there is no adequate, approved, and available alternative to the emergency use of Peramivir IV for the treatment of 2009 H1N1 influenza in certain adult and pediatric patients.

Even though there are a number of limitations to the safety and efficacy data available at this stage of Peramivir IV's development and the data reported are preliminary in nature, based upon the totality of scientific evidence available, it is reasonable to believe that Peramivir IV may be effective in certain patients as specified above.

**Q4. Does the EUA authorize the use of Peramivir IV for the treatment of uncomplicated influenza or prevention of influenza?**

A. No, the EUA states that Peramivir IV will only be authorized for the uses described in Q3. The Fact Sheet for Health Care Providers specifically states "Do not use Peramivir IV for the treatment of seasonal influenza A or B virus infections, for outpatients with acute uncomplicated 2009 H1N1 virus infection or for pre- or post-exposure chemoprophylaxis (prevention) of influenza."

**Q5: Under the EUA, who is authorized to hold and distribute Peramivir IV?**

A. The EUA authorizes only the Centers for Disease Control and Prevention (CDC) to distribute Peramivir IV under its direction to a hospital at the request of the licensed treating clinician. Hospitals that receive Peramivir IV from CDC must, among other things, maintain adequate records showing receipt, use, and disposition of Peramivir IV.

**Q6: Why is this EUA different than the EUAs for Tamiflu and Relenza?**

A. FDA has approved new drug applications for Tamiflu and Relenza and they have been demonstrated to be safe and effective in adequate and well-controlled clinical studies. The EUAs for Tamiflu and Relenza authorize certain unapproved uses of Tamiflu and Relenza, subject to the terms and conditions of the EUAs. Unlike Tamiflu and Relenza, Peramivir IV is not approved by FDA for any use. FDA has concluded (among other things), based on the

totality of scientific evidence available, that it is reasonable to believe that Peramivir IV may be effective in certain patients.

**Q7: What are the specific conditions of authorization for health care providers in the EUA for Peramivir IV?**

Health care providers must follow all the terms and conditions of the EUA for Peramivir IV. The EUA lists eight conditions of authorization that health care providers must follow when using Peramivir IV. The conditions of authorization are summarized below:

- Health care providers will be aware of the EUA, including the terms and conditions as well as any authorized amendments. Health care providers will read the Fact Sheet for Health Care Providers, including the sections on *Mandatory Requirements for Peramivir IV Administration Under Emergency Use Authorization* and *Considerations Prior to Peramivir IV Use Under EUA* as well as any amendments.
- Health care providers prescribing and/or administering Peramivir IV will ensure that the authorized Fact Sheet for Patients and Parents/Caregivers as well as any authorized amendments have been made available to patients and/or parents/caregivers through appropriate means. Health care providers (to the extent practicable given the circumstances of the emergency) will document in the patient's medical record that: (a) patients/caregivers have been given the Fact Sheet for Patients and Parents/Caregivers, (b) patients/caregivers have been informed of the alternatives to receiving authorized Peramivir IV, and (c) patients/caregivers have been informed that Peramivir IV is an unapproved drug that is authorized for use under Emergency Use Authorization.
- Prescribing health care providers (or their designees) will ensure that: (1) selected adverse events and all medication errors associated with the use of authorized Peramivir IV are reported to FDA's MedWatch program; (2) that such reports include in the description section of the MedWatch Form 3500 the words "Peramivir EUA" and include the Peramivir Request number; and (3) that reports are made within seven calendar days from the onset of the event. Moreover, prescribing health care providers or their designees will conduct any follow-up requested by FDA and/or CDC. For detailed information on reporting requirements, see the Information for Healthcare Professionals sheet for mandatory adverse event reporting for emergency use of Peramivir IV under EUA.
- Health care providers will prescribe and/or administer Peramivir IV only for the authorized uses covered in Question # 3.
- Health care providers will ensure that patients with known or suspected renal insufficiency have creatinine clearance determined prior to Peramivir IV dose calculation and first administration.
- Health care providers prescribing and/or administering authorized Peramivir IV will ensure that patients with history of severe allergic reaction to any other neuraminidase inhibitor (zanamivir or oseltamivir phosphate) or any ingredient of Peramivir IV will not receive authorized Peramivir IV.

- Health care providers will only make available additional written information relating to the emergency use of Peramivir IV to the extent that it is consistent with and does not exceed the terms of the EUA (including the Facts Sheets for Patients and Parents/Caregivers).
- Heath care providers will make available to FDA and/or CDC upon request any records maintained in connection with the EUA Letter of Authorization. Upon request, health care providers will report to FDA and/or CDC information with respect to the emergency use of Peramivir IV.

**Q8: Are FDA's Institutional Review Board (IRB)-review and IRB-notification requirements applicable to the emergency use of Peramivir IV (an unapproved, investigational drug) under the EUA?**

A. No, FDA IRB-review and IRB notification requirements are not applicable to the emergency use of Peramivir IV (an unapproved, investigational drug) under the EUA. The terms and conditions for emergency use of Peramivir IV are set forth in the EUA and do not include IRB-review and notification requirements. Health care providers must follow the EUA's terms and conditions of authorization when administering Peramivir IV in order to be within the scope of the EUA. For additional information on EUAs, please review FDA's EUA guidance document.

**Q9. How do health care providers request Peramivir IV under the EUA?**

A. Requests for Peramivir IV are handled by the CDC through the Strategic National Stockpile. Only licensed clinicians with prescribing authority to treat certain hospitalized adult and pediatric patients, as outlined in the Fact Sheet for Health Care Providers, can request Peramivir IV. Hospitals and health care providers conducting activities related to authorized Peramivir IV, such as requesting, preparing, prescribing, and/or administering authorized Peramivir IV, must comply with the terms and conditions of the EUA. Health care providers conducting such activities related to authorized Peramivir IV will read the Fact Sheet for Health Care Providers and any amendments. Peramivir IV can be requested via CDC's Peramivir IV Electronic Request System. Once the completed electronic request has been successfully submitted, acknowledgment will be sent to the email address(es) provided in the request. After the received request has been accepted and processed, a second e-mail notification will be sent. Please note that it may take up to 24 hours, once the decision to ship Peramivir IV is made, for the product to reach the indicated delivery location (i.e., hospital pharmacy).

**Q10. Can health care providers request Peramivir IV for more than one patient?**

A. Yes, Peramivir IV may be requested for more than one patient under the health care provider's care, provided that each patient meets the criteria for treatment with Peramivir IV as described in the Fact Sheet for Health Care Providers. Each request for Peramivir IV to CDC via CDC's Peramivir IV Electronic Request System is discrete for each patient for whom the request is being made. A unique Peramivir Request Number is assigned to each successful request submission. Health care providers should keep the Peramivir Request Number because it is required to be included in adverse event and medication error reports submitted to FDA.

**Q11. Is there any other way health care providers can obtain Peramivir IV for patients other than through the CDC under the Emergency Use Authorization?**

A. Yes, clinical studies of Peramivir IV are currently being conducted. Health care providers considering whether a patient would be appropriate for inclusion in a clinical trial, should review the current Peramivir IV clinical trials at http://www.clinicaltrials.gov.

In special circumstances, Peramivir IV may be obtained using FDA's Emergency Investigational New Drug (E-IND) Application procedures. Special circumstances may include patients who do not meet criteria for Peramivir IV under the EUA or those not eligible to participate in a current Peramivir IV clinical trial.

**Q12. Do the terms and conditions of this EUA apply to health care providers who already have Peramivir IV because they are a clinical site investigator for a Peramivir IV clinical trial or they obtain Peramivir IV under E-IND?**

A. No, the terms and conditions of this EUA apply only to Peramivir IV made available through CDC. Health care providers who receive Peramivir IV because they are a clinical site investigator for a Peramivir IV clinical trial or they obtain the product under an E-IND, should follow the terms of the clinical trial protocol or E-IND protocol and requirements for investigational drugs. Please note that if you request Peramivir IV under this EUA through CDC's Peramivir IV Electronic Request System, you are required to agree that you are responsible for understanding and complying with the terms and conditions of the EUA.

**Q13. There is no expiration date on the vial label of Peramivir IV. How long is this product (the unopened/unused intact vials) good?**

A. Unlike FDA-approved drug products that require a labeled expiration date, an unapproved (investigational) product does not bear a labeled expiration date. However, stability and potency tests are performed by the product's manufacturer at specified time intervals during the development phase of the drug to establish a shelf life. Based on available data reviewed by the FDA, the current lots (Lot #7438, 7439, 7440) of Peramivir IV distributed by CDC can be used up to June 2010, when stored as directed per the terms and conditions of the EUA as described in the Fact Sheet for Health Care Providers. The results of ongoing retesting by the manufacturer will be reviewed by FDA and the above date may be extended. Therefore, unopened/unused intact vials of Peramivir IV product with the above lot numbers should not be discarded in June 2010. Any updated information regarding shelf-life of this product will be provided as appropriate.

**Q14. How is Peramivir IV supplied?**

Peramivir IV is supplied in a 200 mg/20 mL single use vial.

**Q15. How is Peramivir IV stored?**

A. Vials of Peramivir IV should be stored at ambient temperature (15˚C-30˚C or 59˚F-86˚F). Once a diluted solution has been prepared, it should be administered immediately or stored under refrigerated conditions (2˚C-8˚C or 36˚F-46˚F), but should be allowed to reach room temperature prior to administration. The diluted solution should be administered within 24 hours following preparation. Any unused diluted solution must be discarded after 24 hours.

Hospitals must ensure that health care providers acting under the EUA abide by the institutional procedures regarding drug accountability. Hospitals shall maintain adequate records showing receipt, use, and disposition of Peramivir IV.

**Q16. How is Peramivir IV injection prepared?**

A. Please refer to Section 3 *Directions for Preparing Peramivir Injection* in the Fact Sheet for Health Care Providers for detailed directions on preparing doses of Peramivir IV injection for both adult and pediatric patients. Because Peramivir IV is given intravenously, it is necessary to prepare under aseptic conditions and should be inspected visually for particulate matter and discoloration prior to administration.

The calculated amount of Peramivir IV must be diluted in 0.9% or 0.45% Sodium Chloride Injection, USP that does not contain dextrose or other electrolytes. There are no data to support dilution of Peramivir IV with dextrose containing solutions or solutions containing electrolytes other than sodium chloride. It is always recommended to administer intravenous medication immediately after preparation when possible.

**Q17. Can the Fact Sheet for Patients and Parents/Caregivers be translated to a different language?**

A. Under the EUA for Peramivir IV, CDC is authorized to make available additional written information relating to the emergency use of Peramivir IV to the extent that it is consistent with and does not exceed the terms of the EUA. CDC is currently working on translating the Fact Sheet for Patients and Parents/Caregivers into different languages and will make translated versions available on CDC's website: http://www.cdc.gov/h1nflu/eua/Peramivir.htm.

**Q18. Who can health care providers contact if they have more questions or have problems requesting Peramivir IV through CDC's Peramivir IV Electronic Request System?**

A. Health care providers who have further questions or need assistance using CDC's Peramivir IV Electronic Request System or have any clinical questions can contact CDC by calling 1-800-CDC-INFO (1-800-232-4636).

**Q19. What clinical trial information exists for Peramivir IV?**

A. Peramivir IV is an investigational drug and is still being evaluated in phase 3 clinical trials. The available phase 2 and 3 safety and efficacy data for Peramivir IV have been reviewed by FDA. Results from the phase 2 and 3 trials with IV and intramuscular (IM) administration include a statistically significant effect of a single 300 mg or 600 mg IV dose of Peramivir IV compared to placebo in adult patients with acute uncomplicated influenza. Additionally, three phase 2 trials and one phase 3 trial, including one trial in hospitalized patients, did not show statistically significant treatment differences between Peramivir IV and placebo or Tamiflu (oseltamivir phosphate). Even though there are a number of limitations to the safety and efficacy data available at this stage of Peramivir IV's development and the data reported are preliminary in nature, based upon the totality of scientific evidence available, it is reasonable to believe that Peramivir IV may be effective in certain patients.

For more detailed information about the clinical trial experience with Peramivir IV, review the Fact Sheet for Health Care Providers.

**Q20. How many patients have received Peramivir IV?**

A. Approximately 1,891 clinical trial subjects have received Peramivir intravenously (IV) or intramuscularly (IM) at any dose for 1 to 10 days. A total of 478 subjects received a single 600 mg IV dose of Peramivir IV.

Overall, limited multiple dose safety data are available for the intravenous formulation. Only 33 adult clinical trial subjects have received approximately 600 mg (or higher) intravenously once daily for five or more days. No pediatric patients have received Peramivir IV in clinical trials. However, limited use of Peramivir IV in adults and children has been allowed for Peramivir IV 600 mg once daily for 5 to 10 days under emergency IND procedures.

**Q21. Who should not receive Peramivir IV?**

A. Peramivir IV should not be used in patients with a history of severe allergic reaction to any other neuraminidase inhibitors (Relenza or Tamiflu) or any ingredient of Peramivir IV.

Peramivir IV should not be used for treatment of 2009 H1N1 virus infection in patients with documented or highly suspected Tamiflu resistance. The influenza A H1N1 clinical isolates expressing the Tamiflu resistance-associated substitution H275Y appear to be resistant to Peramivir IV.

In addition, as explained under Q4, the Fact Sheet for Health Care Providers specifically states "Do not use Peramivir IV for the treatment of seasonal influenza A or B virus infections, for outpatients with acute uncomplicated 2009 H1N1 virus infection or for pre- or post-exposure chemoprophylaxis (prevention) of influenza."

**Q22. What adverse events associated with Peramivir IV were reported in clinical trials?**

- diarrhea
- nausea
- vomiting
- neutrophil count decreased
- dizziness
- headache
- somnolence
- nervousness
- insomnia
- feeling agitated
- depression
- nightmares
- hyperglycemia
- hyperbilirubinemia
- elevated blood pressure
- cystitis
- anorexia
- proteinuria
- hematuria
- ECG abnormalities (prolonged QTc interval observed in one patient in a phase 1 trial